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LETTERS PATENT
(PATENTS ACT, 1978)

PATENTBRIEF
(WET OP PATENTE, 1978)

No. 73296

WHE
NAD

ELI LILLY AND COMPANY

(Hereinafter called "the Patentee")
(Hieronder "die Patenthouer" genoem)

has applied for the grant of a patent in respect of an invention described and claimed in the complete specification deposited at the Patent Office in Pretoria on the 10th day of February 1981 and in respect of which a provisional patent has been granted.

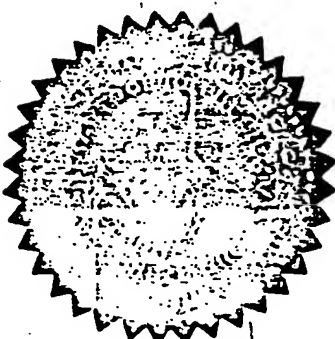
Patent in the name of the Patentee, a copy of which is annexed, together with the relevant Form P. 2; and the Patent Office has granted a patent in respect of the invention described and claimed in the complete specification deposited at the Patent Office in Pretoria on the 10th day of February 1981 and in respect of which a provisional patent has been granted.

BEFORE these Letters Patent are to grant to the Patentee a patent, the effect of which shall be to grant to the Patentee the right to exclude other persons from making, using, or selling the invention, so that he shall have and enjoy the whole profit and advantage accruing by reason of the invention, it is hereby declared that the Patent Office has granted a patent in respect of the invention described and claimed in the complete specification deposited at the Patent Office in Pretoria on the 10th day of February 1981 and in respect of which a provisional patent has been granted.

in the name of the Patentee, a copy of which is annexed, together with the relevant Form P. 2; and the Patent Office has granted a patent in respect of the invention described and claimed in the complete specification deposited at the Patent Office in Pretoria on the 10th day of February 1981 and in respect of which a provisional patent has been granted.

ESTABLISHED BY WHEREOF the seal of the Patent Office has been affixed has been affixed at Pretoria with effect from the 10th day of February 1981 and in respect of which a provisional patent has been granted.

ON the FIFTH day of FEBRUARY nineteen hundred and EIGHTY-ONE



G.P. 572-1978 10 000 (M-L)

Registrar of Patents/Registrars van Patente

(See overleaf)
(Bladsy 2)

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PATENT

1. The patent remains in force only if the required renewal fees are paid annually after the third year of the date of application.
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REPUBLIC OF SOUTH AFRICA

OFFICIAL APPLICATION

21 01

INTERNATIONAL CLASSIFICATION

51

REPUBLIC OF SOUTH AFRICA

REGISTER OF PATENTS

PATENTS ACT, 1978

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FULL NAME(S) OF INVENTOR(S)					
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72 JACK (NMI) MILLS; KLAUS HURT SCHNEGEL and
WALTER NORMAN SHAW

TITLE OF INVENTION	
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54 PHENETHANOLAMINES COMPOSITIONS CONTAINING THE SAME AND
METHOD FOR EFFECTING WEIGHT CONTROL

~~PHENETHANOLAMINE DERIVATIVE FORMULATIONS~~

~~PHENETHANOLAMINE DERIVATIVE FORMULATIONS~~

This invention relates to phenethanolamine derivatives, pharmaceutical formulations containing those compounds, methods of preparing the novel compounds and their use in weight control in mammals.

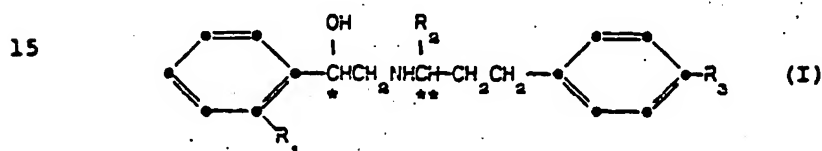
In recent years very extensive research efforts have been effected in the area of β -phenylethylamine derivatives, such as catecholamines. A great deal of study, for example, has been carried out on the naturally occurring catecholamine epinephrine. Epinephrine is a potent sympathomimetic drug and a powerful cardiac stimulant. However, the use of epinephrine is limited because of its undesirable side effects, which include fear, anxiety, tremor, tenseness, throbbing headache, increased blood pressure, dizziness, respiratory difficulty and palpitation, as well as its short duration of action.

Use of drugs which cause more than one biological effect is always potentially dangerous. For example, since both bronchodilation and cardiac stimulation are mediated by the broad group of receptors known as β -receptors, a drug acting on such β -receptors not only would effect bronchodilation, but additionally could cause observable effects upon the heart. In fact, allegedly some individuals have died from ventricular fibrillation caused by excessive β -stimulation after using bronchodilation agents; (See Greenburg and Pines, Br. Med. J. 1, 363(1967)).

The cardiac activity of phenethanolamines has long been known and is well-documented, see for instance U.S. Patent Specification No. 3,816,516.

It has now surprisingly been discovered that the R,S-stereoisomer of certain N-substituted 3-phenylpropylamine derivatives are effective in weight control in obese mammals by removing, or preventing the formation of, excess adipose tissue and further that such compounds possess minimal cardiac activity.

According to the present invention there is provided a compound of the formula (I):



wherein:

- 20 R_1 is hydrogen or fluorine;
 R_2 is methyl or ethyl;
 R_3 is hydroxy, C_1-C_4 alkanoyloxy, amino-carbonyl, methylaminocarbonyl or C_1-C_2 alkoxy-carbonyl;
- 25

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C is an asymmetric carbon atom having the R absolute stereochemical configuration; and

C is an asymmetric carbon atom having the S absolute stereochemical configuration;

5. or a pharmaceutically-acceptable salt thereof.

A preferred group of compounds have the above formula wherein R_2 is methyl.

10. Additionally preferred compounds have the above formula wherein R_1 is hydrogen, R_2 is methyl and R_3 is hydroxy, methoxycarbonyl, aminocarbonyl or methylaminocarbonyl.

15. The most preferred compounds of formula (I) are those wherein R_1 is hydrogen, R_2 is methyl and R_3 is hydroxy or aminocarbonyl, and the pharmaceutically acceptable salts thereof.

- In one aspect of the invention there is provided a pharmaceutical formulation which comprises a compound of formula (I), or a pharmaceutically-acceptable salt thereof, associated with a pharmaceutically-acceptable carrier therefor. A preferred formulation comprises a compound of the above formula wherein R_2 is methyl. An especially preferred pharmaceutical formulation comprises an R,S phenethanclamine of the above formula wherein R_1 is hydrogen, R_2 is methyl and R_3 is hydroxy or aminocarbonyl.
- 20
- 25

Whilst the compounds provided by this invention may be referred to generically as phenethanolamines, they will be systematically named herein as N-substituted-3-phenylpropylamines. The stereochemical configuration of the compounds of this invention is designated according to the R and S nomenclature. A full discussion of this system of nomenclature is presented by Cahn et al., Experientia, Vol. XII, pp. 81-124 (1956). The stereochemical configuration of the carbon atom labeled "C" is R and will be presented first when naming the compounds of the invention. The asymmetric carbon atom labeled "C" has the S absolute stereochemical configuration. Such fact is designated in the systematic naming of such compounds as illustrated for the compound of the above formula wherein R_1 is hydrogen, R_2 is methyl and R_3 is aminocarbonyl: R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-aminocarbonylphenyl)propylamine.

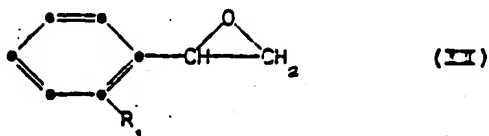
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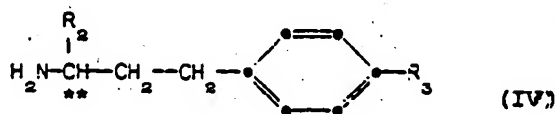
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The compounds provided by this invention can be prepared by any of a number of methods involving well known and routinely used chemical processes. A preferred process involves the reaction of an optically active styrene oxide with an optically active 1-alkyl-3-phenylpropylamine.

According to a further aspect of the invention there is provided a method of preparing a compound of formula (I) in which a styrene oxide of formula (II):



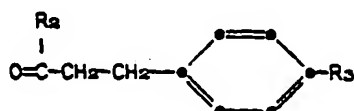
where R_1 is as defined above, is reacted with a propylamine derivative of formula (IV):



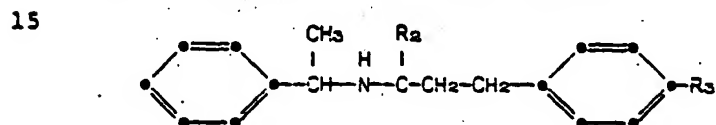
where R_2 and R_3 are as defined above, followed in the case where the styrene oxide is not optically active, i.e. is not the R-styrene oxide, by resolution.

The optically active amines of formula (IV) are novel and are provided in a further aspect of the invention.

They can be prepared from the corresponding ketones of formula:



by reaction with (-)- α -methylbenzylamine in the presence of an acid such as p-toluenesulfonic acid to provide the corresponding S,N-(α -methylbenzyl)-1-(R₂)-3-(4-(R₃)phenyl)-propylimine. Reduction of this imine with Raney nickel gives



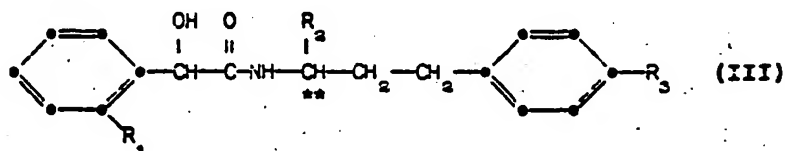
The above amine is salified, for example with HCl, and the salt purified by repeated crystallization from a suitable organic solvent. The optically active S,S-N-(α -methylbenzyl)-1-(R₂)-3-(4-(R₃)phenyl)propylaminium salt thus obtained can then be hydrogenated with palladium on charcoal to remove the α -methylbenzyl group and liberate the amine of formula IV in salt form.

For example, an optically active styrene oxide such as R-ortho-fluorostyrene oxide can be reacted with approximately an equimolar quantity of an optically active phenylpropylamine such as S-1-methyl-3-(4-methylaminocarbonylphenyl)propylamine to provide the corresponding optically active phenethanol-
amine of this invention, namely R,S-N-[2-(2-fluoro-phenyl)-2-hydroxyethyl]-1-methyl-3-(4-methylaminocar-
bonylphenyl)propylamine. Condensation reactions of
this type can be carried out in an unreactive polar
organic solvent such as ethanol, dioxane, toluene or
dimethylformamide, and usually at a temperature of
from about 20 to about 120°C, preferably from 50 to
110°C. Under such conditions, the condensation
generally is substantially complete after about 6 to
about 10 hours, and the product phenethanolamine can
be isolated by simply removing the reaction solvent,
for instance by evaporation under reduced pressure.
Further purification of the product thus formed can
be accomplished if desired by standard methods
including chromatography, crystallization and salt
formation.

Another preferred method for preparing the
compounds of this invention comprises reacting an
optically active mandelic acid derivative with a
phenylpropylamine to provide an amide, and then
reducing the amide carbonyl group to provide a
compound of the invention. Such a method is ideally
suited to the preparation of compounds wherein R₃ is
a hydroxy or alkoxy carbonyl substituent, but is not
preferred for compounds in which R₃ is an amide group
since a mixture of products may result.

According to a further aspect of the invention there is provided a method of preparing a compound of formula (I) which comprises reducing a compound of formula (III)

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where R_1 and R_2 are as defined above and where R_3 is also as defined above or benzyl, followed in the case where R_3 is benzyl by hydrogenolysis of the benzyl group to give the compound of formula (I) where R_3 is hydroxyl, and, where the carbon atom at $-CHOH-$ is unresolved by resolution to the R-enantiomer.

The reaction of the mandelic acid derivative with the phenylpropylamine is best accomplished utilizing coupling reagents such as those commonly used in the synthesis of peptides. Such routinely used coupling reagents include carbodiimides such as N,N'-dicyclohexylcarbodiimide (DCC) and N,N'-diisopropylcarbodiimide, as well as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ). Dicyclohexylcarbodiimide generally is a preferred coupling reagent. A substituted or unsubstituted 1-hydroxybenzotriazole can be employed to accelerate the reaction if desired. The general process for preparing peptides utilizing dicyclohexylcarbodiimide and 1-hydroxybenzotriazole is discussed in detail by König and Geiger in Chem. Ber.,

103, 788-798 (1970). According to such preferred process for preparing a compound of this invention, either R-2-phenyl-2-hydroxyacetic acid or R-2-(2-fluorophenyl)-2-hydroxyacetic acid can be reacted
5 with approximately an equimolar quantity of an optically active S-1-alkyl-3-phenylpropylamine in the presence of a substantially equimolar amount of both dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. The coupling reaction is best carried out in an organic solvent
10 such as dimethylformamide, hexamethylphosphorotriamide, acetonitrile, dichloromethane, and the like. The reaction is normally carried out at reduced temperatures, for example at a temperature below about 50°C., generally at about 0 to about 10°C. The reaction normally is
15 substantially complete within about two to about twenty hours; however, longer reaction periods appear not to be detrimental to the desired product and can be utilized if necessary.

The coupling of an acid and an amine in the
20 presence of dicyclohexylcarbodiimide to form an amide converts the dicyclohexylcarbodiimide to dicyclohexylurea. This latter compound is characteristically quite insoluble in organic solvents and accordingly can be removed from the reaction mixture simply by
25 filtration. Once the dicyclohexylurea is removed from the reaction mixture, the product amide can be isolated by removal of the reaction solvent, for instance by evaporation of the solvent under a reduced pressure. The product thus formed can be dissolved in a water

immiscible organic solvent such as ethyl acetate and washed with aqueous sodium bicarbonate to remove any remaining 1-hydroxybenzotriazole. The amide so formed can, if desired, be further purified by routine procedures including crystallization and chromatography.

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The amide next is reduced to provide the corresponding optically active N-phenylpropyl phenethanolamine comprehended by this invention. Reduction of such amide can be accomplished by any of a number of routine reduction processes, such as reaction with metal hydride reducing agents. A preferred reduction process comprises reaction of an amide with diborane. For example, an amide such as R,S-N-[2-(2-fluorophenyl)-2-hydroxy-1-oxoethyl]-1-ethyl-3-(4-hydroxyphenyl)propylamine can be reduced with diborane to provide a compound of formula (I). In this reduction the diborane typically is utilized in an excess relative to the amide, such as from about 1 to about 4 molar excess. The reduction generally is carried out in an inert organic solvent such as tetrahydrofuran, diethyl ether, benzene, dichloromethane, toluene or dioxane. Such reduction reactions typically are complete within about two to twenty hours when carried out at a temperature of from about 0° to about 100°C. Any excess diborane and borane complex remaining in the reaction mixture after the reduction of the amide is complete can be decomposed by the addition to the reaction mixture of an alcohol such as methanol or ethanol and an acid such as hydrochloric acid. The

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reduced product thus formed can be isolated by simply removing the reaction solvent, for example by evaporation. The product, an optically active phenethanolamine having the above formula, generally
5 exists as a solid and can thus be further purified by crystallization or chromatography. Alternatively, the amine so formed can be converted to an acid addition salt, as will be discussed more fully hereinbelow.

10 It should be recognized that the above-described processes for preparing compounds of formula (I) can be carried out utilizing starting materials unresolved at C, thereby affording mixtures of diastereomers of S,N-phenylpropyl phenethanolamines.
15 Separation of the diastereomers so formed can be accomplished by normal processes when required. Whilst the R-optical isomer of the phenethanol portion of compounds having the above formula (i.e. C) is required for useful biological activity, it is not a major
20 disadvantage to have such R-isomer in admixture with the corresponding S-isomer (i.e. at C), since the S-isomer is substantially devoid of activity and causes no undesired side effects in biological systems at therapeutic doses. However, it is to be clearly
25 understood that this invention comprehends only compounds of formula (I) wherein the asymmetric center

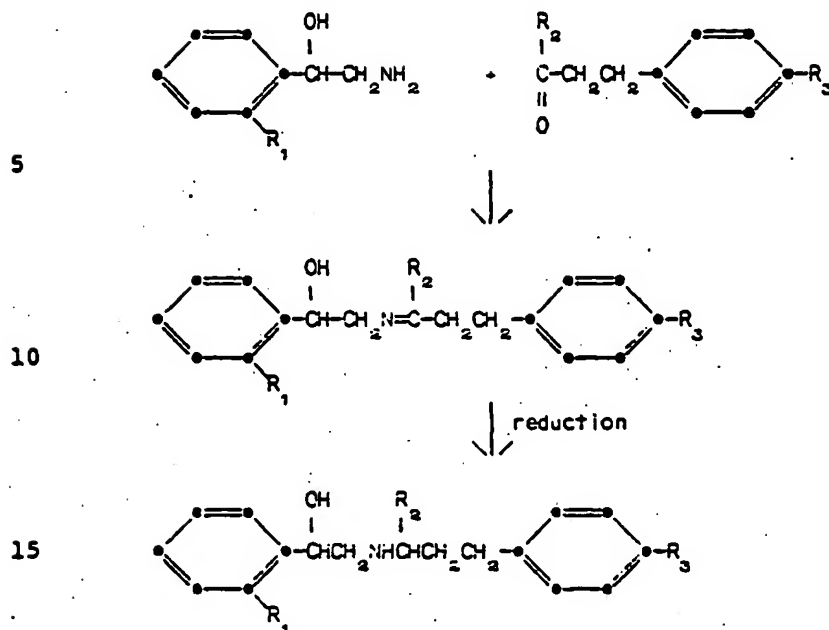
labelled C^{**} has the S absolute stereochemical configuration^{**}, since the R optical isomers (at the C asymmetric center) are potent inotropic agents and cannot be used to treat obesity without simultaneously imparting a significant cardiac effect.

5 Use of the unresolved (at C) material may be particularly desirable if the compounds of the invention are to be utilized in the improvement of the quality of meat in livestock animals, such as
10 cattle, pigs and sheep, by removing, or preventing the formation of, excess adipose tissue therein. The compounds of the invention have particular value in improving the quality of pig carcasses, an animal which tends to fat. In such a method the mixture
15 is preferably applied in an amount of from 5 to 250 mg./kg. per day-usually in the animal's feed.

Another method of preparing compounds of the invention comprises reacting a phenethanolamine with an aldehyde or ketone to provide the corresponding
20 Schiff base, followed by reduction of the Schiff base. Such process is illustrated by the following scheme:

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20 Generally, optically active R-phenethanolamines should be used in the reaction. For example, a compound such as R-2-phenyl-2-hydroxyethylamine can be condensed with an equimolar quantity of a ketone such as methyl 2-(4-ethoxycarbonylphenyl)ethyl ketone. Such condensation of a phenethanolamine and a phenethyl ketone can be carried out in an organic solvent such as

25 toluene, generally in the presence of an acidic catalyst such as para-toluenesulfonic acid. The product from the condensation is an imine, i.e., a Schiff base, which upon reduction provides the corresponding phenethanolamine of the invention. Such

30 reduction typically can be carried out with hydrogen

or with a metal hydride such as sodium cyanoboro-
hydride. The reduction of the imine affords a mixture
of optical isomers at C , the separation of which can
be accomplished utilizing standard resolution
5 techniques such as fractional crystallization.

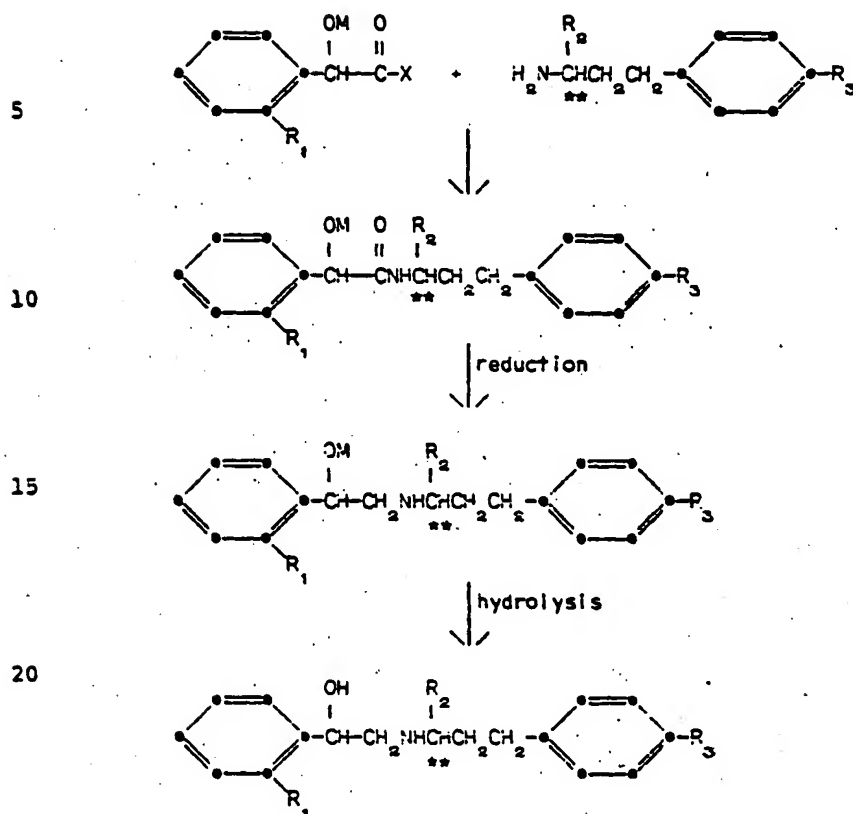
Still another method for preparing the
compounds of this invention comprises reacting a
hydroxy protected 2-phenyl-2-hydroxyacetic acid
acylating agent with an optically active 1-alkyl-3-
10 phenylpropylamine to provide an amide, followed by
reduction of the amide carbonyl group to provide a
compound of this invention. This process may be
depicted by the following reaction scheme:

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25 R_1 , R_2 and R_3 in the above formulae are as defined above, X is a good leaving group and M is a readily removable hydroxy protecting group. Commonly used hydroxy protecting groups include acyl moieties such as acetyl, chloroacetyl and dichloroacetyl, as well as

30 ether forming groups such as trimethylsilyl and the

like. Such readily removable hydroxy protecting groups are more fully described by E. Haslam in Protective Groups in Organic Chemistry, J.F.W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapter 3.

- 5 As noted above, X is defined as a good leaving group and includes halogen radicals such as chloride and bromide, as well as acyloxy groups such as acetoxy and dichloroacetoxy. As an example of the preparation of a compound of this invention utilizing a hydroxy
- 10 protected mandelic acid acylating agent, a compound such as R-2-(2-fluorophenyl)-2-hydroxyacetic acid can be reacted with dichloroacetyl chloride to provide R-2-(2-fluorophenyl)-2-dichloroacetoxyacetic acid. Reaction of this latter compound with a halogenating
- 15 agent such as thionyl chloride or oxalyl chloride provides the corresponding acid chloride, namely R-2-(2-fluorophenyl)-2-dichloroacetoxyacetyl chloride. Reaction of this acid chloride with a phenylpropyl-
- 20 amine, for instance S-1-methyl-3-(4-hydroxyphenyl)-propylamine, provides the corresponding amide, which amide in this case would be R,S-N-[2-(2-fluorophenyl)-2-dichloroacetoxy-1-oxoethyl]-1-methyl-3-(4-hydroxyphenyl)propylamine. The amide so formed is next reduced, for example with diborane, and the hydroxy
- 25 protecting group is removed, for instance by hydrolysis, thus providing an optically active compound of formula (I).

- A further method of preparing compounds of formula (I) comprises reacting a phenacyl halide
- 30 with an optically active S-1-alkyl-3-phenylpropylamine.

For example, a phenacyl halide such as 2-fluoro-phenacyl bromide can be reacted with about an equimolar quantity of an amine such as S-1-methyl-3-(4-hydroxyphenyl)propylamine. Such alkylation reactions are normally carried out in an organic solvent such as ethanol and in the presence of a base such as sodium carbonate or triethylamine. The reaction is complete within about six hours when carried out at about 50°C. and provides a ketone intermediate, for instance S-N-[2-(2-fluorophenyl)-2-oxoethyl]-1-methyl-3-(4-hydroxyphenyl)propylamine. The ketone thus formed can be isolated as the free amine base or as an acid addition salt. Reduction of the ketone, for example with sodium borohydride, affords a compound of formula (I), generally as a mixture of optical isomers at C. Such a mixture of R, S and S,S optical isomers can be separated by standard procedures, or if desired can be utilized directly since the S,S isomer is essentially devoid of biological activity.

Compounds having the above formula wherein R_3 is hydroxyl, that is compounds of this invention which bear a phenolic hydroxyl group, can be readily acylated to provide compounds having the above formula in which R_3 is C_1-C_4 alkanoyloxy. As used herein, the term " C_1-C_4 alkanoyloxy" includes formyloxy, acetoxy, propionyloxy, butyryloxy, and isobutyryloxy. The acylation of a compound of this invention having a phenolic hydroxyl group typically is accomplished by reacting

the hydroxyl compound with an acylating agent such as the appropriate acid anhydride or acid halide for example the acid chloride or acid bromide. Typical acylating agents commonly employed include acetic anhydride, propionyl chloride, isobutyryl bromide and formic-acetic anhydride.

It may be desirable to protect the hydroxyl and amino groups of the phenethanolamine portion of the compound of this invention prior to acylation of the free phenolic hydroxyl group, thereby precluding any undesired side reactions. For example, a compound of this invention such as R,S-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-1-ethyl-3-(4-hydroxyphenyl)propylamine can be reacted with thionyl chloride in the presence of a base such as triethylamine and in a solvent such as tetrahydrofuran to form a cyclic oxathiazole, thus effectively protecting both the hydroxyl group and the amino group of the phenethanolamine portion of the molecule. Such reaction converts the above-named compound into R,S-N-[1-ethyl-3-(4-hydroxyphenyl)propyl]-5-(2-fluorophenyl)-1-oxo-4,5-dihydro-1,2,3-oxathiazole. This latter compound can then be acylated at the free phenolic hydroxyl functionality without risk of affecting other sites in the molecule. For instance, R,S-N-[1-ethyl-3-(4-hydroxyphenyl)propyl]-5-(2-fluorophenyl)-1-oxo-4,5-dihydro-1,2,3-oxathiazole can be reacted with an acylating agent such as acetic anhydride or acetyl chloride in a solvent such as benzene, xylene or toluene and in the presence of a base such

as triethylamine, generally at a temperature of about 50° to 100°C., thus effecting acylation of the phenolic hydroxyl group to provide R,S-N-[1-ethyl-3-(4-acetoxyphe-
5 nyl)propyl]-5-(2-fluorophenyl)-1-oxo-4,5-dihydro-1,2,3-oxathiazole. The oxathiazole thus prepared is treated with an acid such as a dilute mineral acid to re-
move the protecting groups and thus recover the desired phenethanolamine. For example, the above-named
oxathiazole can be treated with 1 N hydrochloric acid
10 at a temperature of about 30°C. to provide R,S-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-1-ethyl-3-(4-acetoxyphe-
nyl)propylamine as the acid addition salt, which upon treatment with a base such as sodium carbonate affords a free amine of formula (I).

15 Compounds of the formula (I) wherein R_3 is aminocarbonyl can be prepared either directly by reacting the appropriate phenylpropylamine with a styrene oxide or alternatively can be derived from those compounds wherein R_3 is C_1 - C_2 alkoxy carbonyl
20 such as methoxycarbonyl or ethoxycarbonyl. For example, R-mandelic acid can be coupled with S-1-methyl-3-(4-methoxycarbonylphenyl)propylamine to provide, after reduction of the amide carbonyl, the corresponding amine of this invention, namely R,S-N-(2-phenyl-2-
25 hydroxyethyl)-1-methyl-3-(4-methoxycarbonylphenyl)-propylamine. This amine can be reacted with hydrazine for about 2 to 40 hours at about 50 to 100°C. to convert the alkoxy carbonyl group to a hydrazino carbonyl group. The latter compound is converted by

hydrogenation to the corresponding aminocarbonyl derivative, utilizing common hydrogenation catalysts such as Raney nickel.

Compounds of formula (I) wherein R_3 is methylaminocarbonyl are preferably prepared by reacting a styrene oxide with a 3-(4-methylaminocarbonylphenyl)propylamine. The required phenylpropylamine starting material can be prepared by simply reacting methylamine with the appropriate benzoyl chloride derivative. For example, S-1-ethyl-3-(4-chlorocarbonylphenyl)propylaminium chloride can be reacted with methylamine to provide S-1-ethyl-3-(4-methylaminocarbonylphenyl)propylamine. Reaction of the latter compound with a styrene oxide affords a compound of this invention.

The compounds provided by this invention are amines and as such are basic in nature. Consequently, they can readily be converted to acid addition salts by reaction with organic or inorganic acids. Accordingly, an additional embodiment of this invention

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comprises pharmaceutically acceptable salts of the N-phenylpropyl phenethanolamines of the above formula. The particular acids utilized to form salts of this invention are not critical, and such salts include
5 those which are prepared by reaction of the amine of this invention with any of a number of common acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, formic, acetic, butyric, citric, maleic, succinic, oxalic, fumaric, lactic, methane-
10 sulfonic, p-toluenesulfonic, and related acids. The pharmaceutically acceptable acid addition salts which are formed by reaction of an amine of this invention with an acid such as one of the above-named acids typically exist as highly crystalline solids, and thus
15 lend themselves to ready purification by recrystallization from common solvents such as methanol, ethanol, ethyl acetate and the like. Additionally, such salts are easily formulated for convenient administration, particularly by the oral route, to
20 subjects in need of treatment for obesity. When desired, such acid addition salts are readily converted to the corresponding free amine base by reaction with a suitable basic compound, for instance sodium or potassium hydroxide, sodium carbonate, triethylamine,
25 sodium bicarbonate, and the like.

The following list of compounds is provided to illustrate the range of compounds comprehended by this invention. The representative listing is not intended to be inclusive of every compound claimed
30 herein, but rather simply illustrates certain preferred compounds and the relative scope of the disclosure.

- R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
3-(4-hydroxyphenyl)propylamine;
- R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
3-(4-aminocarbonylphenyl)propylamine;
- 5 R,S-N-(2-phenyl-2-hydroxyethyl)-1-ethyl-
3-(4-hydroxyphenyl)propylamine;
- R,S-N-(2-phenyl-2-hydroxyethyl)-1-ethyl-
3-(4-aminocarbonylphenyl)propylamine;
- R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
10 3-(4-methylaminocarbonylphenyl)propylamine;
- R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
3-(4-acetoxyphenyl)propylamine;
- R,S-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-
1-methyl-3-(4-ethoxycarbonylphenyl)propylamine;
- 15 R,S-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-
1-ethyl-3-(4-methoxycarbonylphenyl)propylamine;
- R-N-(2-phenyl-2-hydroxyethyl)-3-(4-methylamino-
carbonylphenyl)propylamine;
- R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
20 3-(4-isobutyroxyphenyl)propylamine;
- R,S-N-(2-phenyl-2-hydroxyethyl)-1-ethyl-3-
(4-methylaminocarbonylphenyl)propylamine;
- R-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-
3-(4-ethoxycarbonylphenyl)propylamine;
- 25 R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
3-(4-ethoxycarbonylphenyl)propylamine;
- R-N-(2-phenyl-2-hydroxyethyl)-3-(4-amino-
carbonylphenyl)propylamine;
- R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
30 3-(4-hydroxyphenyl)propylaminium chloride;

R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
3-(4-methylaminocarbonylphenyl)propylaminium bromide;

R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
3-(4-hydroxyphenyl)propylaminium acetate;

5 R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
3-(4-hydroxyphenyl)propylaminium butyrate;

R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-
3-(4-aminocarbonylphenyl)propylaminium succinate;

Obesity is a very serious disease that
10 currently is the subject of a great deal of concern,
particularly since no truly effective treatments are
known. A full discussion of nutritional diseases and
obesity in general is presented by Albrink in Textbook
15 of Medicine, 12th Ed., 1969, W. B. Saunders Company,
Philadelphia, Pa., pp. 1164-1174 and by Salans in
Current Therapy, 1977, W. B. Saunders Company, pp.
455-460. Compounds provided by this invention are
particularly useful due to their ability to effect an
20 actual reduction in weight when administered to a
mature obese animal. Such weight reduction is accom-
plished without a concomitant reduction in daily food
consumption. When the compounds of this invention are
administered to immature obese animals, the degree of
weight gain is significantly reduced compared to that
25 observed in young obese animals not receiving a
compound of the invention.

The anti-obesity activity of the compounds
of this invention has been demonstrated in a number of
biological tests utilizing mice, rats and dogs. One
30 of the major actions of the claimed compounds on a

biological system appears to be the mobilization of fatty acids from adipose tissue stores. In a test designed to demonstrate such mobilization, a compound of this invention was administered to a total of eight
5 normal fed rats of the Charles River strain, each weighing about 180 to 200 grams. A blood sample from each animal was taken immediately preceding the administration of the test compound and served as the control for each of the eight animals. A compound of
10 this invention was then administered to each animal subcutaneously at the dose of 10 mg./kg. of body weight. Blood samples were then taken from each animal at intervals of 30, 60, 90 and 120 minutes after dosing, and the serum free fatty acid levels
15 were determined for each blood sample. Table I presents the results of such test carried out with two compounds of this invention. The results demonstrate that a dramatic increase in serum free fatty acid levels is caused by a compound of this invention.

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Table I

	Average % of serum free fatty acid rise after dosing
25 R,S-N-(2-phenyl-2-hydroxy)- 1-methyl-3-(4-hydroxy- phenyl)propylamine	425%
R,S-N-(2-phenyl-2-hydroxy- ethyl)-1-methyl-3-(4-amino- carbonylphenyl)propylamine	350%

30 In a test designed to demonstrate the actual weight reducing effects of the compounds of this invention, viable yellow genetically obese mice were

selected as a model. All of the animals were 6.5 months old at the beginning of the study. The animals were fed Purina Laboratory Chow and water ad libitum throughout the study. Five obese animals were randomly selected to receive 10 mg./kg. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propyl-amine subcutaneously twice daily, and five animals received placebo. The initial body weight of each animal was determined on day 1 of the study prior to the first injections. Table II presents the results of the study. The data is presented as the average body weight in grams of the control group and of the group receiving the test compound. Such average body weight in grams is presented in column I under each of the indicated days. Column II under each of the indicated days provides the average food consumption in grams for the control group and for the test group.

The results presented in Table II demonstrate that the compounds of this invention cause an actual reduction in body weight in mature obese animals without causing a decrease in food consumption.

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Table II

	Day I	Day 10	Day 20	Day 30	Day 40	Day 50
	I II	I II	I II	I II	I II	I II
Control group receiving placebo	50 3.2	50 4.8	51 5.1	50 5.0	50 4.0	51 4.0
test group receiving drug	48 3.0	43 4.8	40 5.0	37 5.0	36.5 4.4	37 4.5

A similar study was carried out utilizing genetically obese Zucker rats. The compounds of the invention effected a dramatic weight reduction without decreasing daily food consumption when administered to adult obese rats (6 months and older). When administered to immature obese rats ranging in age from 2 to 5 months, the compounds were effective in preventing the excessive gain in weight as was observed with the young obese rats which did not receive a compound of this invention. Table III presents the results of a study carried out by administering R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propylamine at 10 mg./kg. twice daily to the test animals. All animals were permitted to eat all the food and drink all the water they wanted. The food consumption of the animals given a compound of the invention did not differ significantly from the control animals receiving placebo. Each of the body weights reported in the table is the average weights of five animals in each of the test classes.

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Table III

	Day 1	Day 20	Day 40	Day 60	Day 80
	body weight in grams	body weight in grams	body weight in grams	body weight in grams	body weight in grams
Immature Zucker controls	490	500	525	550	570
Immature Zucker rats receiving drug	475	480	482	478	485
Mature Zucker controls	629	631	630	625	629
Mature Zucker rats receiving drug	632	625	595	575	560

The anti-obesity drugs provided by this invention additionally have demonstrated their ability to effect weight reductions in obese dogs. Obese breeder beagles from the Pin Oak colony ranging in age from 4 to 9 years and weighing from 15.4 to 29.0 kg. were selected for the test. The dogs were fed ad libitum a Eucanuba diet containing sixteen percent fat for six months prior to the initiation of the study, thereby stabilizing the dogs' obesity. In one test, the animals received R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propylaminium chloride at a subcutaneous dose of 3.2 mg./kg. twice each day. The effect of the drug on body weight was determined by measuring body weight in kilograms. No decrease in food consumption was noted. The results of five weeks treatment are summarized in Table IV.

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Table IV

	Weight in Kg.		Weight loss Kg.	percent weight loss
	Day 1	Day 35		
Dog 1	17.2	15.8	1.4	8%
Dog 2	29.2	25.5	3.7	12.5%
Dog 3	18.7	16.5	2.2	12%
Dog 4	16.2	15.0	1.2	7.5%

In a similar test utilizing mature obese beagle hounds, fed ad libitum on standard dog chow, R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-amino-carbonylphenyl)propylaminium chloride was administered orally at 15 mg./kg. twice daily for twenty-seven days. The effect of the drug on body weight was determined by measuring body weight in kilograms and girth size in inches. Two dogs were selected as control animals receiving food and water ad libitum, but no drug. Table V presents the results of the test. As the data demonstrates, the control dogs did not fluctuate a great deal in weight or girth size. In contrast, the obese dogs treated with a compound of this invention lost from 1.8 to 2.9 kilograms during a 27 day treatment period, and the girth of such obese dogs decreased by as much as 2 inches in the same period of time.

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Table V

	Day 1		Day 7		Day 14		Day 21		Day 27	
	Weight	girth	Weight	girth	Weight	girth	Weight	girth	Weight	girth
	kg.	inches	inches	size	inches	size	inches	size	inches	size
Control animal	16.7	24	16.2	24.5	16.9	24.5	16.2	25	16.4	25
Control animal	16.3	25	16.4	25	16.5	24	16.5	24	16.5	25
Test animal	20.4	27.5	20.5	27	19.5	27	18.1	27	17.5	25.5
Test animal	17.7	26	16.9	26	16.7	25.5	15.9	26	15.9	25
Test animal	20.7	26	20.0	26	19.7	25.5	19.8	25	18.6	25

As already pointed out, the unique physiological effect of the compounds of this invention is derived from their potent anti-obesity activity coupled with their physiologically tolerable degree of cardiovascular activity. This uniquely specific activity is achieved by selecting the correct, i.e. R,S-, stereochemistry at both the asymmetric carbon atoms of the compound of formula (I).

5 The unique physiological activity of the R,S-isomers of this invention compared with the corresponding R,R-isomers (which are potent inotropic agents) has been demonstrated in dogs. The compounds to be evaluated were administered intravenously to dogs having implanted cardiovascular transducers for measurement of the derivative of the left ventricular pressure, which is the index of cardiac contractile force. A dose of compound sufficient to cause a twenty-five percent increase in contractile force was administered. The dose required to effect such increase in contractile force is reported in Table VI as the ED₂₅ in mcg./kg. The results demonstrate that very little of the inotropically active R,R-isomers is required to effect a twenty-five percent increase in contractile force, whereas a significantly larger dose of the corresponding R,S-isomer is required to cause the same effect.

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Table VI

	Compound administered	Contractile Force ED ₂₅ mcg./kg.
5	R,S-N-(2-phenyl-2-hydroxy-ethyl)-1-methyl-3-(4-hydroxy-phenyl)propylamine	100.0
	R,R-N-(2-phenyl-2-hydroxy-ethyl)-1-methyl-3-(4-hydroxy-phenyl)propylamine	2.5
10	R,S-N-(2-phenyl-2-hydroxy-ethyl)-1-methyl-3-(4-amino-carbonylphenyl)propylamine	100.0
	R,R-N-(2-phenyl-2-hydroxy-ethyl)-1-methyl-3-(4-amino-carbonylphenyl)propylamine	3.0

15 Because of the surprisingly low inotropic activity of the compounds of this invention, they can be administered to an animal at doses large enough to effect release of free fatty acids from adipose stores without causing a substantial increase in the pumping

20 force of the heart. Such unique biological spectrum of the compounds of this invention renders them particularly useful in the control of weight in obese animals. As used herein, "weight control in obese animals" refers to the ability of the compounds of

25 this invention to effect an actual weight reduction when administered to a mature obese animal, whereas such compounds are effective in the prevention of excessive weight gain when administered to immature obese animals. The terms "mature" and "immature" are

30 used herein to refer to the generally accepted definitions of age and growth patterns. "Obesity" is an art recognized term and is used as such herein.

An additional aspect of this invention is a method for controlling weight in obese animals. While the anti-obesity effective dose of a compound of this invention employed in the control of obesity will vary
5 depending on the particular drug employed and the severity of the condition being treated, the usual dosage of a compound of this invention will be from about 1.0 to about 25 mg. per kilogram of animal body weight. The compounds of the invention preferably
10 will be administered orally at a dosage of from about 1 to about 5 mg./kg., generally given in individual doses from one to four times per day. When desired, the drug can be administered orally in the form of a tablet or capsule, or alternatively in sustained
15 release form. According to the method of this invention a compound defined by the above general formula is administered to a mature obese animal to effect an actual reduction in weight without diminishing the daily food consumption. The drug will be administered
20 daily, at increasing dosage levels if desired, until the desired weight reduction is effected. The compounds of the invention can be administered to an immature obese animal to effect a reduction in weight gain without a diminished daily food consumption.
25 Once the immature obese animal reaches maturity, a reduction of weight will be effected until a substantially normal weight is achieved.

The compounds comprehended by this invention can be formulated by normal procedures for convenient
30 administration by any of a number of routes. It is preferred that the compounds be formulated for oral administration. Pharmaceutical formulations which are

useful in weight control in obese animals are provided in a further embodiment of this invention.

Such pharmaceutical compositions can contain, as active ingredient, one or more of the compounds provided by this invention, in combination if desired with any of the inactive isomers as hereinbefore indicated, in addition to any of a number of pharmaceutically acceptable carriers or diluents. Typical carriers and diluents commonly used include gelatin, starch, dextrose, sucrose, lactose, cellulose derivatives, stearates, polyvinylpyrrolidone, glycerine, ethyl lactate, sorbitol, mannitol, and the like. A suitable pharmaceutical composition can additionally include any of a number of common preserving agents, stabilizers, antioxidants, taste correctors, and the like. Examples of such additives include ascorbic acid, sorbic acid, various esters of p-hydroxybenzoic acid, and the like.

Typical pharmaceutical compositions useful in the treatment of obesity according to this invention will generally include from about 1 to about 50 percent by weight of a compound of this invention as active ingredient. The remainder of said pharmaceutical composition will comprise suitable carriers and diluents, and any of the indicated inactive optical isomers as desired.

A pharmaceutical composition containing as active ingredient at least one of the compounds of this invention can be molded into tablets, encapsulated into empty gelatin capsules, or made into a solution

or suspension. Such pharmaceutical compositions can be administered to an obese subject in need of treatment by any of a number of routes, including the oral and parenteral routes. A preferred formulation, for example, comprises about 250 mg. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-aminocarbonylphenyl)-propylaminium chloride admixed with any of a number of suitable carriers and molded into a tablet for oral administration to an obese human subject at the rate of from 1 to about 4 tablets per day for effective weight control.

In an effort to more fully illustrate particular aspects of this invention, the following Preparations illustrate how starting materials useful in the invention may be prepared whereas the following Examples illustrate the preparation of final products of formula (I). The Examples are representative only and should not be construed as limiting in any respect.

Preparation 1

Preparation of R-styrene oxide

To a cold stirred solution of 300 g. of R-mandelic acid in 2000 ml. of tetrahydrofuran was added dropwise over two hours 3000 ml. of a 1 molar solution of diborane in tetrahydrofuran. The reaction mixture was stirred for twelve hours at 25°C. following complete addition, and then was cooled to 0°C. in an ice water bath. To the cold solution was added 600 ml. of methanol dropwise over thirty minutes, and the reaction mixture was then stirred for another three

hours. Removal of the solvent by evaporation under reduced pressure provided 260 g. of the product as a solid. The solid was crystallized from diethyl ether to provide R-2-phenyl-2-hydroxyethanol.

- 5 A solution of 256.7 g. of R-2-phenyl-2-hydroxyethanol in 1000 ml. of toluene containing 50 ml. of pyridine was stirred at 0°C. while a solution of 372.1 g. of p-toluenesulfonyl chloride in 400 ml. of toluene was added dropwise over two hours.
- 10 The reaction mixture was stirred at 0°C. for forty-eight hours and then filtered to remove the precipitated pyridine hydrochloride. The filtrate was concentrated to dryness by evaporation under reduced pressure to provide the product as an oil. The oil
- 15 was dissolved in fresh toluene, washed with dilute hydrochloric acid and with water, and dried. Evaporation of the solvent under reduced pressure and crystallization of the product from diethyl ether and hexane afforded 435 g. of R-2-phenyl-2-hydroxy-
- 20 1-p-toluenesulfonyloxyethane. The product thus formed was dissolved in 1000 ml. of dimethyl sulfoxide containing 418 ml. of 5 N sodium hydroxide. The alkaline solution was stirred at 0°C. for twelve hours, and then was poured into ice water. The
- 25 product was extracted into 50% diethyl ether-pentane, and the organic layer was separated, washed with water and dried. Removal of the solvent by evaporation afforded, after distillation, 165 g. of R-styrene oxide. B.P. 55-56°C. 0.6 torr. $[\alpha]_D -23.7^\circ$ (chloro-
- 30 form).

Preparation 2

Preparation of R-ortho-fluorostyrene oxide

One hundred three grams of dl-o-fluoro-
5 mandelic acid was resolved by reaction with (+)-
α-methylbenzylamine to form the salt, and crystal-
lization of the salt from ethanol and ethyl acetate
to provide optically active α-methylbenzylaminium
2-(2-fluorophenyl-2-hydroxy)acetate, M.P. 155-157°C.
10 [α]_D -43.1° (MeOH). The salt thus formed was
hydrolyzed to the free acid to provide R-ortho-
fluoromandelic acid, M.P. 88-90°C. [α]_D -138° (MeOH).
The acid was then converted to R-ortho-fluorostyrene
oxide by the procedure of Preparation 1, B.P.
15 58-61°C. (3 torr), [α]_D -32.7° (chloroform).

Preparation 3

Preparation of S-1-methyl-3-(4-aminocarbonyl-
phenyl)propylamine

20 The oil from 280 g. of a 50% dispersion of
sodium hydride in mineral oil was removed by several
washings with hexane. The hexane was replaced with
1.5 l. of dimethylformamide, and the mixture was
stirred and cooled in an ice-bath while 950 g. of
25 ethyl acetoacetate was slowly added. After the
sodium hydride had reacted a solution of 314 g. of
α-bromo-p-toluic acid in 500 ml. of dimethylform-
amide was added. The ice bath was removed and the
mixture was allowed to stir at 25°C. for eighteen
30 hours, poured into water acidified with 3N hydro-
chloric acid and extracted with ethyl acetate. The

combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. The solvent and excess ethyl acetoacetate were removed at reduced pressure to afford 500 g. of oil.

5 The crude oil was combined with 1.2 l. of glacial acetic acid, 140 ml. of concentrated hydrochloric acid and 750 ml. of water and heated at refluxed for three and one half hours. The solvents were removed under reduced pressure and the residue
10 was dissolved in a mixture of ether and xylene and washed with water. The solid obtained after removal of the solvents was recrystallized twice from a mixture of ethanol and water to give 111 g. of 4-(4-carboxyphenyl)-2-butanone, m.p. 120.5-123°C.

15 Analysis calc. for $C_{11}H_{12}O_3$
 Theory: C, 68.74; H, 6.29.
 Found : C, 68.99; H, 6.10.

 A mixture of 9.50 g. of 4-(4-carboxyphenyl)-
20 2-butanone, 100 ml. of benzene, 15.7 g. of oxalyl chloride and one drop of dimethylformamide was stirred and warmed to 50°C. for two hours. The reaction mixture was then allowed to stir for
25 eighteen hours at 25°C. and concentrated under reduced pressure. The residue was dissolved in 50 ml. of dioxane and, with stirring, was added slowly to 300 ml. of cold (0°C.) concentrated
ammonium hydroxide. The mixture was stirred for seventy-five minutes and diluted to 1 l. with water.
30 The solid was removed by filtration, washed with water, dried and recrystallized from a mixture of

methanol and ether to provide 4.1 g. of 4-(4-aminocarbonylphenyl)-2-butanone, m.p. 144-146°C. An analytical sample, m.p. 149-150°C., was obtained by recrystallizing twice from a mixture of methanol and ether.

Analysis calc. for $C_{11}H_{13}NO_2$
Theory: C, 69.09; H, 6.85; N, 7.32.
Found : C, 68.98; H, 7.10; N, 6.99.

10 A solution of 45.7 g. of 4-(4-amino-
carbonylphenyl)-2-butanone in 400 ml. of toluene
containing 29.0 g. of (-)- α -methylbenzylamine and
1.0 g. of p-toluenesulfonic acid was heated at
15 reflux for four hours with removal of water via a
Dean Stark trap. After cooling the reaction mixture
to room temperature, the solvent was removed there-
from by evaporation under reduced pressure to provide
S-N-(α -methylbenzyl)-1-methyl-3-(4-aminocarbonyl-
phenyl)-propylimine. The imine was hydrogenated in
20 625 ml. of methanol utilizing 15 g. of Raney Nickel

as the catalyst to provide a mixture of optical isomers of N-(α -methylbenzyl)-1-methyl-3-(4-aminocarbonylphenyl)propylamine. The amine was reacted with hydrogen chloride to provide the corresponding acid addition salt as a solid. The mixture was purified by repeated crystallization of the salt from methanol and acetonitrile to provide 23.6 g. of optically active S,S-N-(α -methylbenzyl)-1-methyl-3-(4-aminocarbonylphenyl)propylaminium chloride. M.P. 256-258°C. $[\alpha]_D -80.1^\circ$ (MeOH).

A solution of 16.3 g. of the salt in 480 ml. of ethanol containing 3.0 g. of five percent palladium suspended on carbon was hydrogenated for twenty-two hours at 50°C. under a pressure of 60 p.s.i. The reaction mixture then was filtered and the solvent was removed from the filtrate by evaporation under reduced pressure to provide the product as a solid. The solid was recrystallized three times from ethanol and ethyl acetate to afford 9.4 g. of S-1-methyl-3-(4-aminocarbonylphenyl)propylaminium chloride. M.P. 237-240°C. $[\alpha]_D -8.2$ (MeOH).

Analysis calc. for $C_{11}H_{17}ClN_2O$

Theory: C, 57.76; H, 7.49; N, 12.25

Found: C, 57.65; H, 7.57; N, 12.10

Preparation 5

S-1-Methyl-3-(4-aminocarbonylphenyl)propylamine

To 213 g. of (S)-(-)- α -methylbenzylamine in
1 l. of benzene was added 290 g. of 4-(4-hydroxy-
phenyl)-2-butanone and 0.5 g. of p-toluenesulfonic
acid. The reaction mixture was stirred and heated to
reflux. The water that was formed during the re-
action was azeotropically removed. After the
theoretical amount of water had separated, the
benzene was removed at reduced pressure, and the
residue was dissolved in methanol and hydrogenated in
the presence of Raney nickel at ambient temperature
over a sixteen hour period. The catalyst was removed
by filtration, and the methanol and any unreacted
 α -methylbenzylamine were removed at reduced pressure.
The residue was dissolved in 500 ml. of ethanol and
an excess of hydrogen chloride in ether was added.
The solid that formed was filtered, washed with
ether, and recrystallized from a mixture of ethanol
and acetone. Several more recrystallizations from a
mixture of methanol and acetonitrile gave 263 g. of
S,S-N-(α -methylbenzyl)-1-methyl-3-(4-aminocarbonyl-
phenyl)propylamine, hydrochloride, m.p. 180-182°C.
[α]_D -72.2, [α]₃₆₅ -257.5° (MeOH).

A mixture of 258 g. of the above-named
hydrochloride salt, 26 g. of 5 percent palladium on
carbon and 1700 ml. of ethanol was hydrogenated at
60°C. for eight and one half hours. The catalyst was
removed by filtration and the solvent was evaporated.

-40B-

The residue was dissolved in hot ethanol, ether was added and 149 g. of crystalline title product was removed by filtration, m.p. 198-202°C., $[\alpha]_D$ -8.5, $[\alpha]_{365}$ -23.5° (MeOH).

Example 1

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-3-(4-methylaminocarbonylphenyl)propylamine

5 To a refluxing solution of 3.6 g. of
S-1-methyl-3-(4-methylaminocarbonylphenyl)propylamine
in 50 ml. of ethanol was added dropwise over ten
minutes a solution of 2.1 g. of R-styrene oxide in
20 ml. of ethanol. Following complete addition of
10 the styrene oxide, the reaction mixture was heated at
reflux for four hours and then cooled to 25°C. and
stirred at that temperature for twelve hours. The
solvent was next removed by evaporation under reduced
pressure to provide an oil which was then crystal-
15 lized from diethyl ether to provide 3.5 g. of the
product as a solid. The solid was recrystallized
from ethyl acetate and diethyl ether to afford 1.7 g.
of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-
methylaminocarbonylphenyl)propylamine. M.P. 158-
20 160°C.

The amine so formed was converted to the
hydrochloride salt by reaction with hydrogen chloride
in diethyl ether to provide, following crystallization
from methanol and ethyl acetate, 1.2 g. of R,S-
25 N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-methyl-
aminocarbonylphenyl)propylaminium chloride. M.P.
179-182°C.

Analysis calc. for $C_{20}H_{27}ClN_2O_2$

Theory: C, 66.19; H, 7.50; N, 7.72.

Found: C, 66.40; H, 7.82; N, 7.49.

30

Example 2

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-ethyl-3-(4-hydroxyphenyl)propylamine

5 A solution of 7.16 g. of (S)-1-ethyl-3-(4-hydroxyphenyl)propylamine in 50 ml. of N,N-dimethylformamide (DMF) was cooled in an ice-water bath and stirred under a nitrogen gas atmosphere while a solution of 6.08 g. of R-mandelic acid and
10 5.41 g. of 1-hydroxybenzotriazole in 15 ml. of DMF was added in one portion. A solution of 8.24 g. of dicyclohexylcarbodiimide in 10 ml. of DMF was added dropwise over thirty minutes to the stirred reaction mixture. The reaction mixture was stirred for two
15 hours at 5°C., and then allowed to set for twelve hours at 0°C. Dicyclohexylurea had precipitated out of solution, and was separated from the reaction mixture by filtration. Removal of the solvent from
20 the filtrate by evaporation under reduced pressure provided a solid residue. The solid was purified by washing it with sodium carbonate followed by crystallization from acetonitrile to provide 7.31 g. of R,S-N-(2-phenyl-2-hydroxy-1-oxoethyl)-1-ethyl-3-(4-hydroxyphenyl)propylamine. M.P. 116-118.5°C.
25 $[\alpha]_D -61^\circ$ (MeOH).

Analysis calc. for $C_{19}H_{23}NO_3$

Theory: C, 72.82; H, 7.40; N, 4.47.

Found: C, 72.73; H, 7.22; N, 4.77.

30 A solution of 6.17 g. of the amide thus formed in 70 ml. of tetrahydrofuran (THF) was added dropwise over one hour to a stirred solution of

60 ml. of 1 molar diborane in THF. Following the addition, the reaction mixture was stirred at 24°C. under a nitrogen gas atmosphere for forty-eight hours. Excess methanol then was added to the re-
5 action mixture in order to decompose any unreacted diborane. The solvents were removed from the reaction mixture by evaporation under reduced pressure to provide the product as an oil. The oil so formed was dissolved in ethyl alcohol and diethyl ether, and
10 excess hydrogen chloride gas was bubbled through the reaction mixture in order to form the hydrogen chloride acid addition salt. The salt precipitated out of solution and was removed therefrom by filtration. The solid product so formed was recrystallized several times from ethyl acetate to afford
15 171 mg. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-ethyl-3-(4-hydroxyphenyl)propylaminium chloride. M.P. 148-151°C. $[\alpha]_D -25.0^\circ$ (MeOH).

Analysis calc. for $C_{19}H_{26}ClNO_2$
20 Theory: C, 67.94; H, 7.80; N, 4.17.
Found: C, 67.97; H, 7.72; N, 4.45.

Example 3

R,S-N-[2-(2-Fluorophenyl)-2-hydroxyethyl]-1-
25 methyl-3-(4-hydroxyphenyl)propylamine

A solution of 15.05 g. of S-1-methyl-3-(4-benzyloxyphenyl)propylamine in 50 ml. of DMF was cooled in an ice-water bath and stirred under a nitrogen gas atmosphere while a solution of 10.0 g.
30 of R-2-(2-fluorophenyl-2-hydroxy)acetic acid and

7.97 g. of 1-hydroxybenzotriazole in 50 ml. of DMF was added in one portion. The reaction mixture was stirred at 5°C. while a solution of 12.15 g. of dicyclohexylcarbodiimide in 20 ml. of DMF was added dropwise over thirty minutes. The reaction mixture was stirred at 5°C. for one hour, and then allowed to stand at 9°C. for twelve hours. Dicyclohexylurea had precipitated out of solution, and was removed from the reaction mixture by filtration. The filtrate was diluted with ethyl acetate, washed with sodium carbonate, and then concentrated by evaporation of the solvent under reduced pressure, thus providing 23.0 g. of R,S-N-[2-(2-fluorophenyl)-2-hydroxy-1-oxoethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine as an oil.

To a stirred solution of 15.2 g. of lithium aluminum hydride in 800 ml. of diethyl ether was added dropwise over one hour a solution of 23.0 g. of the amide thus formed in 100 ml. of THF. After the addition was complete, the reaction mixture was heated at reflux for six hours, and then stirred for an additional twelve hours at 24°C. Any unreacted lithium aluminum hydride remaining in the reaction mixture was decomposed by the dropwise addition of 16 ml. of water, followed by the addition of 12 ml. of twenty percent aqueous sodium hydroxide solution and 56 ml. of water. Filtration and removal of the solvents from the reaction mixture by evaporation under reduced pressure provided R,S-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylamine. The residue so formed was dissolved in

ethyl alcohol and diethyl ether, and excess hydrogen chloride gas was bubbled through the solution. The precipitate which formed was collected by filtration and recrystallized twice from ethyl alcohol and
5 diethyl ether, affording 10.0 g. of R,S-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-1-methyl-3-(4-benzyloxyphenyl)propylaminium chloride. M.P. 162-163°C.

Analysis calc. for $C_{25}H_{29}ClFNO_2$
10 Theory: C, 69.84; H, 6.80; N, 3.26.
Found: C, 70.04; H, 6.95; N, 3.41.

A solution of 10.0 g. of the salt thus formed in 190 ml. of ethyl alcohol containing 2.0 g. of a suspension containing five percent of palladium
15 on carbon was heated at 50°C. and stirred for two hours under a hydrogen gas atmosphere at 50 p.s.i. The reaction mixture then was cooled to room temperature and filtered. The filtrate was concentrated by evaporation of the solvent under reduced pressure,
20 thus affording, after crystallization twice from ethanol and ether, 6.9 g. of R,S-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylaminium chloride. M.P. 180-183°C.
[α]_D -40.6° (MeOH).

25 Analysis calc. for $C_{18}H_{23}ClFNO_2$
Theory: C, 63.62; H, 6.82; Cl, 10.43;
F, 5.54; N, 4.12.
Found: C, 63.44; H, 6.81; Cl, 10.63;
F, 5.38; N, 4.27.

30

Example 4

R,S-N-[2-(2-Fluorophenyl)-2-hydroxyethyl]-1-ethyl-3-(4-hydroxyphenyl)propylamine

5 A solution of 11.62 g. of S-1-ethyl-3-(4-hydroxyphenyl)propylamine in 50 ml. of DMF was cooled in an ice-water bath and stirred under a nitrogen gas atmosphere while to it was added in one portion a solution of 11.0 g. of R-2-(2-fluoro-
10 phenyl-2-hydroxy)acetic acid in 20 ml. of DMF containing 8.78 g. of 1-hydroxybenzotriazole. The reaction mixture was stirred at 5°C. while a solution of 13.39 g. of dicyclohexylcarbodiimide in 15 ml. of DMF was added dropwise over thirty minutes. Fol-
15 lowing complete addition of the dicyclohexylcarbodiimide solution, the reaction mixture was stirred at 5°C. for two hours, and then was stored at 0°C. for an additional seventy-two hours. Dicyclohexylurea precipitated out of solution and was removed
20 from the reaction mixture by filtration. The filtrate was concentrated by evaporation of the solvent under reduced pressure to provide an oil. The oil was dissolved in 200 ml. of ethyl acetate, and washed with dilute aqueous hydrochloric acid solution, with
25 aqueous sodium carbonate solution, and with water. The solution was dried and the solvent was removed therefrom by evaporation under reduced pressure to provide R,S-N-[2-(2-fluorophenyl)-2-hydroxy-1-oxoethyl]-1-ethyl-3-(4-hydroxyphenyl)propylamine as a
30 solid. M.P. 114-118°C.

A solution of 13.0 g. of the above-named amide derivative in 100 ml. of tetrahydrofuran (THF) was added dropwise over one hour to a stirred solution of 105 ml. of 1 molar diborane in THF.

- 5 Following complete addition of the amide derivative, the reaction mixture was stirred for six hours at 24°C., and then was cooled to 0°C. and allowed to set for twelve hours. The reaction mixture was next warmed to room temperature and stirred while excess
- 10 methanol was added to decompose any unreacted diborane remaining in the reaction mixture. Evaporation of the reaction solvent under reduced pressure then provided R,S-N-(2-(2-fluorophenyl)-2-hydroxyethyl)-1-ethyl-3-(4-hydroxyphenyl)propyl-
- 15 amine as an oil. The oil so formed was dissolved in ethanol, and diethyl ether containing excess hydrogen chloride gas was added. The hydrochloride salt of the above-named amine precipitated out of solution, and was recovered by filtration. Recrystallization
- 20 of the solid so formed from ethanol and diethyl ether afforded R,S-N-(2-(2-fluorophenyl)-2-hydroxyethyl)-1-ethyl-3-(4-hydroxyphenyl)propylaminium chloride. M.P. 121-124°C. $[\alpha]_D -27.3^\circ$ (MeOH).

Analysis calc. for $C_{19}H_{25}ClFNO_2$

- 25 Theory: C, 64.49; H, 7.12; Cl, 10.02;
F, 5.37; N, 3.96.
Found: C, 64.58; H, 6.91; Cl, 10.16;
F, 5.47; N, 4.11.

Example 5

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propylamine

5 A solution of 122.0 g. of S-1-methyl-
3-(4-hydroxyphenyl)propylamine in 300 ml. of DMF was
cooled to 5°C. in an ice-water bath and stirred while
a solution of 112.6 g. of R-mandelic acid and 100.0 g.
10 of 1-hydroxybenzotriazole in 300 ml. of DMF was added
in one portion. The reaction mixture was stirred at
5°C. while a solution of 156.0 g. of dicyclohexyl-
carbodiimide in 500 ml. of DMF was added dropwise
over two hours. Following the complete addition of
the dicyclohexylcarbodiimide, the reaction mixture
15 was stirred for an additional fifteen minutes, and
then was allowed to set at 0°C. for twelve hours.
The reaction mixture then was filtered to remove the
precipitated dicyclohexylurea. Next, the solvent was
removed from the reaction mixture by evaporation
20 under reduced pressure, leaving an oily residue. The
oil so formed was dissolved in 1000 ml. of ethyl
acetate and washed with aqueous sodium carbonate and
water. After drying the solution, the solvent was
removed by evaporation under reduced pressure, thus
25 providing 205.8 g. of R,S-N-(2-phenyl-2-hydroxy-1-
oxoethyl)-1-methyl-3-(4-hydroxyphenyl)propylamine.
The amide thus formed was recrystallized from ethyl
acetate and hexane. M.P. 219-223°C. $[\alpha]_D -54.1^\circ$
(MeOH).

30

Analysis calc. for $C_{18}H_{21}NO_3$

Theory: C, 72.22; H, 7.07; N, 4.68.

Found: C, 71.98; H, 6.79; N, 4.89.

5 A solution of 168.2 g. of the amide and
170 ml. of triethylamine in 3000 ml. of benzene and
700 ml. of THF was stirred at 24°C. while 143 ml. of
trimethylchlorosilane was added portionwise. The
reaction mixture was stirred for thirty minutes and
10 then filtered to remove the precipitated triethyl-
amine hydrochloride. The filtrate was concentrated
by evaporation of the solvent under reduced pressure,
leaving an oily residue. The oil was next dissolved
in 1000 ml. of THF, and the solution was stirred at
15 24°C. under a nitrogen gas atmosphere while 1300 ml.
of 1 molar diborane in THF was added portionwise.
The reaction mixture was stirred at room temperature
for sixteen hours, and then excess methanol was added
to the solution in order to decompose any unreacted
20 diborane and to hydrolyze the trimethylsilyl ester.
Removal of the solvent by evaporation under reduced
pressure provided an oil. The oil was dissolved in
diethyl ether containing hydrogen chloride, and the
salt which formed was collected by filtration and
25 recrystallized from ethanol and diethyl ether,
affording 131.0 g. of R,S-N-(2-phenyl-2-hydroxy-
ethyl)-1-methyl-3-(4-hydroxyphenyl)propylaminium
chloride. M.P. 149-150.5°C. $[\alpha]_D -51.7^\circ$ (MeOH).

30

Example 6

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propylamine

5 A solution of 10.4 g. of S-1-methyl-3-(4-benzyloxyphenyl)propylamine in 150 ml. of DMF was stirred at room temperature under a nitrogen gas atmosphere while 6.35 g. of R-mandelic acid and 5.63 g. of 1-hydroxybenzotriazole were added. The
10 reaction mixture was cooled to -5°C. in an ice and methanol bath and stirred while a solution of 9.03 g. of dicyclohexylcarbodiimide in 70 ml. of DMF was added dropwise over ten minutes. The reaction mixture then was stirred at 5°C. for one hour and
15 then stored at 0°C. for twelve hours. The reaction mixture next was filtered, thus removing the precipitated dicyclohexylurea. The filtrate was concentrated by evaporation of the solvent under reduced pressure to provide an oily residue. The oil
20 so formed was dissolved in 400 ml. of benzene and washed with aqueous sodium carbonate solution, with 1 N hydrochloric acid solution, and with water. After drying the reaction mixture, the solvent was removed by evaporation under reduced pressure,
25 providing 13.6 g. of R,S-N-(2-phenyl-2-hydroxy-1-oxoethyl)-1-methyl-3-(4-benzyloxyphenyl)propylamine as a crystalline solid. M.P. 102-104.5°C. $[\alpha]_D -48.98^\circ$ (MeOH).

30 Analysis calc. for $C_{25}H_{27}NO_3$
Theory: C, 77.09; H, 6.99; N, 3.60.
Found: C, 76.87; H, 7.03; N, 3.65.

A solution of 110 ml. of 1 molar diborane in THF was diluted with an additional 100 ml. of THF. The solution was cooled in an ice-acetone bath and stirred under a nitrogen gas atmosphere while a
5 solution of 12.3 g. of R,S-N-(2-phenyl-2-hydroxy-1-oxoethyl)-1-methyl-3-(4-benzyloxyphenyl)propylamine in 75 ml. of THF was added dropwise over twenty minutes. The reaction mixture was heated at reflux for four hours, and then cooled to room temperature
10 and stirred for an additional twelve hours. Excess methanol next was added to the reaction mixture in order to decompose any unreacted diborane. Concentration of the reaction mixture by evaporation of the solvent under reduced pressure provided an oily
15 residue. The oil was dissolved in 100 ml. of methanol and 100 ml. of diethyl ether. The solution was stirred and hydrogen chloride was bubbled through the solution, thus forming a precipitate. The precipitate was collected by filtration and recrystallized from acetonitrile. The crystalline solid so
20 formed was suspended in ethyl acetate and washed with sodium carbonate and water. After drying the ethyl acetate solution, the solvent was removed by evaporation under reduced pressure, thus affording
25 R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-benzyloxyphenyl)propylamine. M.P. 113-115.5°C. $[\alpha]_D$ -17.5° (MeOH).

Analysis calc. for $C_{25}H_{29}NO_2$

Theory: C, 79.96; H, 7.78; N, 3.73.

30 Found: C, 79.74; H, 7.82; N, 3.43.

A solution of 5.9 g. of the amine thus formed in 50 ml. of methanol was stirred at 24°C. while a solution of excess hydrogen chloride gas in diethyl ether was added in one portion. The precipitated solid which immediately formed was collected by filtration and then was recrystallized from acetonitrile and diethyl ether, providing 6.39 g. of the amine as the hydrochloride salt. M.P. 158.0-160.5°C. $[\alpha]_D -36.1^\circ$ (MeOH).

Analysis calc. for $C_{25}H_{30}ClNO_2$
Theory: C, 72.89; H, 7.34; N, 3.40.
Found: C, 72.91; H, 7.34; N, 3.27.

A solution of 10.6 g. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-benzyloxyphenyl)-propylaminium chloride in 140 ml. of methanol was stirred while 1.0 g. of a five percent suspension of palladium on carbon was added portionwise. The reaction mixture then was stirred for four hours at 60°C. under a hydrogen gas atmosphere at 50 p.s.i. The reaction mixture then was filtered, and the filtrate was concentrated by evaporation of the solvent under reduced pressure, thus providing 10.6 g. of a pink foam. The foam was dissolved in 500 ml. of water and stirred while a solution of 35 g. of sodium carbonate in 300 ml. of water was added portionwise over ten minutes. The product precipitated out of the aqueous alkaline solution and was collected by filtration. Recrystallization of the solid product so formed twice from 450 ml. of hot ethyl acetate provided 6.63 g. of R,S-N-(2-phenyl-

2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propyl-
amine. M.P. 169.5-173°C. $[\alpha]_D -24.5^\circ$ (MeOH).

Analysis calc. for $C_{18}H_{23}NO_2$

Theory: C, 75.76; H, 8.12; N, 4.91.

Found: C, 75.99; H, 8.11; N, 4.68.

Example 7

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-3-
(4-hydroxyphenyl)propylaminium chloride

A solution of 6.63 g. of the free amine
from Example 6 in 200 ml. of methanol was stirred
while a solution of hydrogen chloride in diethyl
ether was added in one portion. The solvent was
removed by evaporation under reduced pressure to
provide the product as a white solid. The solid was
collected by filtration and then was recrystallized
from acetone and diethyl ether to afford R,S-
N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydroxy-
phenyl)propylaminium chloride. M.P. 150-159°C.
 $[\alpha]_D -47.0^\circ$ (MeOH).

Analysis calc. for $C_{18}H_{24}ClNO_2$

Theory: C, 67.17; H, 7.52; N, 4.35;

Cl, 11.02.

Found: C, 66.97; H, 7.29; N, 4.50;

Cl, 11.32.

Example 8

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-3-
(4-acetoxyphenyl)propylamine

A solution of 6.03 g. of R,S-N-(2-phenyl-
2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propyl-

amine dissolved in 350 ml. of tetrahydrofuran and 200 ml. of benzene was stirred at room temperature while 9.05 g. of triethylamine was added in one portion. The reaction mixture was stirred while a
5 solution of 4.97 g. of thionyl chloride in 100 ml. of benzene was added dropwise over eight minutes. An additional 3.62 g. of triethylamine dissolved in 50 ml. of benzene was added to the reaction mixture, and then the reaction mixture was stirred for two
10 hours at room temperature. The reaction mixture was washed several times with aqueous saturated sodium bicarbonate solution, and then with water. The solvent was removed from the reaction mixture by evaporation under reduced pressure to provide 8.1 g.
15 of R,S-N-[1-methyl-3-(4-hydroxyphenyl)propyl]-5-phenyl-1-oxo-4,5-dihydro-1,2,3-oxathiazole as an orange oil.

A solution of 3.6 g. of the above-named oil in 20 ml. of benzene was stirred at room temperature while 1.5 ml. of pyridine was added, followed by the
20 addition to the reaction mixture of 1.15 ml. of acetic anhydride. The reaction mixture was refluxed and stirred for one hour. The reaction mixture was cooled to room temperature and allowed to stand for
25 twelve hours. The reaction mixture was next poured into 50 ml. of xylene, and the solvents were then removed by evaporation under reduced pressure to provide an oil. The oil was chromatographed over
25 g. of alumina, eluting with benzene and 80%
30 benzene in ethyl acetate. Collection of the appro-

priate fractions and evaporation of the solvent therefrom gave 2.41 g. of an oil. A solution of 2.41 g. of the oil in 50 ml. of ethyl alcohol containing 4.5 ml. of 3 N hydrochloric acid was
5 stirred for fifteen minutes at room temperature. The reaction mixture was then poured into 50 ml. of xylene, and the solvents were removed by evaporation under reduced pressure, providing 2.17 g. of a solid residue. Crystallization from ethyl acetate of the
10 solid residue thus formed provided 1.77 g. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-acetoxyphe-nyl)propylaminium chloride. M.P. 160-161°C.
[α]_D -44° (MeOH).

Analysis calc. for $C_{20}H_{26}ClNO_3$
15 Theory: C, 66.02; H, 7.20; N, 3.85;
Cl, 9.74.
Found: C, 65.92; H, 7.31; N, 3.86;
Cl, 9.78.

Example 9

20 R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-3-(4-isobutyroxyphenyl)propylamine

A solution of 4.5 g. of R,S-N-[1-methyl-3-(4-hydroxyphenyl)propyl]-5-phenyl-1-oxo-4,5-di-
25 hydro-1,2,3-oxathiazole in 40 ml. of benzene was stirred at room temperature while 4.0 ml. of pyridine and 2.85 g. of isobutyric anhydride were added in one portion. The reaction mixture was stirred and heated at reflux for sixteen hours. The reaction mixture
30 was cooled and diluted with xylene, and the solvents

were removed by evaporation under reduced pressure, providing 4.36 g. of an oil. The oil so formed was dissolved in 8 ml. of 3 N hydrochloric acid, and the mixture was stirred for fifteen minutes at room temperature. The reaction mixture was next poured into 50 ml. of xylene, and concentrated to dryness under reduced pressure, providing 4.34 g. of a solid residue. The solid thus formed was crystallized from acetonitrile to afford 3.75 g. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-isobutyroxyphenyl)-propylaminium chloride. M.P. 158.5-160°C. $[\alpha]_D -41.6^\circ$ (MeOH).

Analysis calc. for $C_{22}H_{30}ClNO_3$
Theory: C, 67.42; H, 7.72; N, 3.57;
Cl, 9.05.
Found: C, 67.61; H, 8.01; N, 3.74;
Cl, 9.16.

Example 10

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-3-(4-methoxycarbonylphenyl)propylamine

Methyl 2-(4-hydroxycarbonylphenyl)ethyl ketone was esterified by reaction with methyl alcohol and hydrochloric acid to provide methyl 2-(4-methoxycarbonylphenyl)ethyl ketone. The ketone was condensed with optically active S- α -methylbenzylamine, and the imine which was formed was reduced to provide N-(α -methylbenzyl)-1-methyl-3-(4-methoxycarbonylphenyl)propylamine. The amine was converted to the hydrochloride salt, and fractional crystal-

lization of the salt thus formed afforded optically active S,S-N-(α -methylbenzyl)-1-methyl-3-(4-methoxycarbonylphenyl)propylaminium chloride. M.P. 198-205°C. $[\alpha]_D -81.2^\circ$ (MeOH).

5 The resolved α -methylbenzyl protected aminium chloride was hydrogenated in the presence of Raney nickel to effect removal of the α -methylbenzyl protecting group, thus providing optically active S-1-methyl-3-(4-methoxycarbonylphenyl)propylaminium
10 chloride. M.P. 165-172°C. $[\alpha]_D -6.7^\circ$ (MeOH).

A solution of S-1-methyl-3-(4-methoxycarbonylphenyl)propylaminium chloride in ethyl acetate was reacted with aqueous sodium carbonate to provide 4.8 g. of S-1-methyl-3-(4-methoxycarbonylphenyl)propylamine. The optically active free amine
15 was dissolved in a solution of 150 ml. of N,N-dimethylformamide containing 3.52 g. of R-mandelic acid and 3.4 g. of 1-hydroxybenzotriazole. The reaction mixture was stirred while a solution of
20 4.78 g. of N,N'-dicyclohexylcarbodiimide in 50 ml. of DMF was added dropwise over twenty minutes. Following the complete addition of the dicyclohexylcarbodiimide, the reaction mixture was cooled to about 10°C. and stored for twelve hours at that temperature.
25 The dicyclohexylurea which had precipitated out of the reaction solution was removed by filtration, and the filtrate was concentrated to dryness by evaporation of the solvent under reduced pressure to provide an oil. The oil so formed was dissolved in ethyl
30 acetate and washed with aqueous sodium carbonate,

with water, and dried. Evaporation of the solvent under reduced pressure afforded an oil which was crystallized from diethyl ether and hexane to provide 6.27 g. of R,S-(2-phenyl-2-hydroxy-1-oxoethyl)-1-methyl-3-(4-methoxycarbonylphenyl)propylamine. 5 M.P. 99-101°C. $[\alpha]_D -59.2^\circ$ (MeOH).

Analysis calc. for $C_{20}H_{23}NO_4$

Theory: C, 70.36; H, 6.79; N, 4.10.

Found: C, 70.57; H, 6.85; N, 4.21.

10 The above reactions were repeated on several occasions to provide additional quantities of the amide. To a stirred solution of 26.2 g. of R,S-N-(2-phenyl-2-hydroxy-1-oxoethyl)-1-methyl-3-(4-methoxycarbonylphenyl)propylamine in 300 ml. of 15 tetrahydrofuran was added portionwise over one hour 400 ml. of a 1.02 N solution of diborane in tetrahydrofuran. Following the addition, the reaction mixture was stirred at 25°C. for twenty-six hours. The reaction mixture next was diluted by the addition 20 of 250 ml. of methanol. Removal of the reaction solvent by evaporation under reduced pressure provided the product as a crude oil. The oil was dissolved in 50 ml. of fresh methanol, and the solution was diluted with 100 ml. of diethyl ether 25 saturated with hydrogen chloride, thereby forming the hydrochloride salt of the product as a white solid. The solid was recrystallized from 100 ml. of acetonitrile to provide 15.60 g. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-methoxycarbonylphenyl)- 30 propylaminium chloride. M.P. 141-155°C. The salt

was converted to the free amine base which was crystallized from ethyl acetate. M.P. 125-128°C. The free base was converted to the hydrochloride salt, which when crystallized from acetonitrile and diethyl ether afforded the desired product having a

5 M.P. 149-154°C. $[\alpha]_D -48.8^\circ$ (MeOH).

Analysis calc. for $C_{20}H_{26}ClNO_3$

Theory: C, 66.02; H, 7.20; N, 3.85.

Found: C, 65.91; H, 6.96; N, 3.78

10

Example 11

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-3-(4-aminocarbonylphenyl)propylamine

A solution of 1.21 g. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-methoxycarbonylphenyl)-propylamine in 60 ml. of ethyl alcohol containing 20 ml. of anhydrous hydrazine was stirred and heated at reflux for twenty-eight hours. The reaction mixture then was cooled to room temperature and the solvent was removed therefrom by evaporation under reduced pressure to provide a product which was crystallized from isopropanol to give 940 mg. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydrazinocarbonylphenyl)propylamine. M.P. 134-142°C.

25 $[\alpha]_D -27.9^\circ$ (MeOH).

Analysis calc. for $C_{19}H_{25}N_3O_2$

Theory: C, 69.70; H, 7.70; N, 12.83.

Found: C, 69.72; H, 7.44; N, 12.97.

30



A solution of 720 mg. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydrazinocarbonyl-phenyl)propylamine in 100 ml. of ethanol containing 8 g. of Raney nickel was hydrogenated in a Brown
5 hydrogenation apparatus utilizing 4 g. of sodium borohydride as the hydrogen source. The reaction mixture was stirred at 25°C. for twelve hours, and then was filtered through hyflo super cell. The filtrate was evaporated to dryness under reduced
10 pressure to provide a solid. The solid residue thus formed was dissolved in 50 ml. of water containing 25 ml. of 3 N hydrochloric acid. The aqueous acid solution was washed with ethyl acetate, and then made basic by the gradual addition of ammonium hydroxide.
15 The aqueous alkaline solution was extracted several times with fresh portions of ethyl acetate. The organic extracts were combined, washed with water and dried. Removal of the solvent by evaporation under reduced pressure provided, as a white solid, R,S-
20 N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-amino-carbonylphenyl)propylamine. The solid thus formed was dissolved in methanol and the solution was diluted with 30 ml. of diethyl ether saturated with hydrogen chloride. Filtration of the precipitated
25 solid which formed afforded 72.6 mg. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-aminocar-bonylphenyl)propylaminium chloride. M.P. 229-230°C. $[\alpha]_D -51.6^\circ$ (MeOH).

Analysis calc. for $C_{19}H_{25}ClN_2O_2$
Theory: C, 65.41; H, 7.22; N, 8.03;
Cl, 10.16.
Found: C, 65.29; H, 7.14; N, 8.24;
Cl, 10.04.

Example 12

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-
3-(4-aminocarbonylphenyl)propylaminium chloride

10 To a refluxing solution of 109.6 g. of
S-1-methyl-3-(4-aminocarbonylphenyl)propylamine in
600 ml. of ethanol and 200 ml. of methanol was added
dropwise over one hour a solution of 68.4 g. of
R-styrene oxide in 100 ml. of ethanol. The reaction
15 mixture was heated at reflux for three hours fol-
lowing complete addition of the styrene oxide, and
then was cooled to room temperature and concentrated
by evaporation of the solvent under reduced pressure.
The reaction mixture next was diluted by the addition
20 of 200 ml. of diethyl ether and filtered. The
precipitate was triturated with water, dried, and
recrystallized from acetonitrile to provide 72.6 g.
of the free amine product as a solid. The amine so
formed was converted to the hydrochloride salt by
25 reaction with hydrogen chloride in diethyl ether to
provide 64.0 g. of R,S-N-(2-phenyl-2-hydroxyethyl)-
1-methyl-3-(4-aminocarbonylphenyl)propylaminium
chloride. M.P. 229-231°C. $[\alpha]_D -52.1^\circ$ (MeOH).

30 Analysis calc. for $C_{19}H_{25}ClN_2O_2$
Theory: C, 65.41; H, 7.22; N, 8.03.
Found: C, 65.17; H, 7.10; N, 8.03.

Example 13

R,S-N-(2-Phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propylamine

5 A mixture of 100 g. of R-mandelic acid and
244 ml. of dichloroacetyl chloride was heated at 60°C.
and stirred for three hours. The mixture then was
cooled to room temperature and concentrated in volume
under reduced pressure to provide a yellow oil. The
10 oil was dissolved in 200 ml. of thionyl chloride, and
the reaction mixture was heated to reflux and stirred
for four hours. The reaction mixture was cooled to
room temperature and excess thionyl chloride was
removed by evaporation under reduced pressure. The
15 product was purified by distillation to provide
180.9 g. of R-(2-phenyl-2-dichloroacetoxy)acetyl
chloride. B.P. 112.5°C. (0.08 torr); $[\alpha]_D -191^\circ$
(toluene).

 A solution of 4.3 g. of S-1-methyl-3-(4-
20 benzyloxyphenyl)propylamine in 70 ml. of dichloro-
methane was added in one portion to a stirred
suspension of 5.5 g. of sodium bicarbonate and
5.02 g. of R-(2-phenyl-2-dichloroacetoxy)acetyl
chloride in 100 ml. of dichloromethane. The reaction
25 mixture was stirred at room temperature for sixteen
hours and then filtered. The filtrate was concen-
trated by evaporation of the solvent under reduced
pressure to provide a solid residue. The residue was
crystallized from 75 ml. of diethyl ether to afford
30 6.70 g. of R,S-N-(2-phenyl-2-dichloroacetoxy-1-

oxoethyl)-1-methyl-3-(4-benzyloxyphenyl)propylamine.

M.P. 110-111.5°C. $[\alpha]_D -41.7^\circ$ (MeOH).

Analysis calc. for $C_{27}H_{27}Cl_2NO_4$

Theory: C, 64.80; H, 5.44; N, 2.80;

5 Cl, 14.17.

Found: C, 64.66; H, 5.61; N, 2.94;

Cl, 14.42.

A solution of 6.70 g. of the amide thus
formed in 130 ml. of tetrahydrofuran containing
10 50 ml. of 1 N diborane in tetrahydrofuran was heated
to reflux and stirred for twenty hours. The reaction
mixture was cooled to 60°C. and decomposed by the
dropwise addition of 2 ml. of water and 35 ml. of 3 N
hydrochloric acid. The aqueous acidic mixture was
15 heated to reflux for two hours, again cooled to about
40°C., and then made alkaline by the addition of
100 ml. of 5 N sodium hydroxide. After stirring the
alkaline mixture for two hours at room temperature,
the organic layer was separated and the aqueous
20 alkaline layer was extracted with ethyl acetate. The
organic layers were combined, washed with brine,
dried and the solvent was evaporated to provide
5.1 g. of a solid residue. The solid was dissolved
in 100 ml. of hot ethanol and acidified by the
25 addition of a diethyl ether solution of hydrogen
chloride. The crystalline precipitate which formed
was collected by filtration and dried to provide
4.40 g. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-
methyl-3-(4-benzyloxyphenyl)propylaminium chloride.
30 M.P. 160-162.5°C. $[\alpha]_D -37.8^\circ$ (MeOH).

Analysis calc for $C_{25}H_{30}ClNO_2$

Theory: C, 72.89; H, 7.34; N, 3.40;
Cl, 8.61.

Found: C, 73.02; H, 7.58; N, 3.64;
Cl, 8.96.

5

Hydrogenolysis of 4.28 g. of the amine salt thus formed in the presence of 500 mg. of five percent palladium on carbon in methanol for three hours at 40°C. effected removal of the benzyl protecting group to provide, after purification by crystallization from acetone and diethyl ether, 2.79 g. of R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propylaminium chloride. M.P. 153-154°C. $[\alpha]_D -49.9^\circ$ (MeOH).

10

15

Analysis calc. for $C_{18}H_{24}ClNO_2$

Theory: C, 67.17; H, 7.52; N, 4.35;
Cl, 11.02.

Found: C, 67.08; H, 7.33; N, 4.51;
Cl, 11.37.

20

Example 14

Preparation of 250 mg. Tablets

25

R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-aminocarbonylphenyl)-propylaminium chloride 250 mg.

Lactose 200 mg.

Corn Starch 300 mg.

Corn Starch Paste 50 mg.

30

Calcium Stearate 5 mg.

Dicalcium Phosphate 45 mg.

The active drug, corn starch, lactose, and dicalcium phosphate are uniformly blended. The corn starch paste is prepared as a 10 percent aqueous paste and is blended into the mixture to uniformity.

5 The mixture is blended with the calcium stearate and then compressed into tablets. Such tablets can be administered to an obese subject at the rate of 1 to about 4 tablets per day or as needed.

Example 15

10

Preparation for Suppositories

R,S-N-(2-phenyl-2-hydroxyethyl)-1-methyl-3-(4-hydroxyphenyl)propyl-aminium chloride 500 mg.

15

Theobroma oil 1500 mg.

20

The above ingredients are blended to uniformity at a temperature of about 60°C. and then permitted to cool in a tapered mold. Each suppository will weigh about 2 grams and can be administered to a mature obese subject from 1 to 2 times each day for the reduction of weight, or to an immature obese subject for the control of weight gain.

25

30

Example 16

Preparation for Oral Suspension

5	R,S-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylaminium acetate	5000 mg.
	Sorbitol solution (70% N.F.)	40 mg.
	Sodium benzoate	150 mg.
10	Lactose	10 mg.
	Cherry flavor	50 mg.
	Distilled water q.s. ad	100 ml.

15 The sorbitol solution is added to 40 ml. of distilled water and the R,S-N-[2-(2-fluorophenyl)-2-hydroxyethyl]-1-methyl-3-(4-hydroxyphenyl)propylaminium acetate is dissolved therein. The lactose, sodium benzoate and flavoring are added and dissolved. The volume of the solution is adjusted to 100 ml.

20 with distilled water. Each ml. of syrup contains 50 mg. of active drug. A mature obese mammal will be administered about 5 to about 20 ml. of syrup each day for the effective loss of weight.

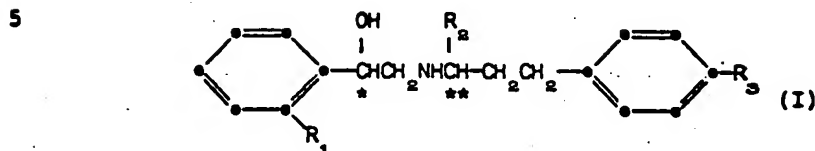
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30

...
...
...
to be part of, ... *we* ... *claim* ...

-67-

1. An optically active compound of the formula (I)



wherein:

- 10 R_1 is hydrogen or fluorine;
 R_2 is methyl or ethyl;
 R_3 is hydroxy, C_1 - C_4 alkanoyloxy, amino-carbonyl, methylaminocarbonyl or C_1 - C_2 alkoxy-carbonyl;
15 C^* is an asymmetric carbon atom having the R absolute stereochemical configuration; and
 C^{**} is an asymmetric carbon atom having the S absolute stereochemical configuration; or
20 a pharmaceutically acceptable salt thereof.
2. A compound according to Claim 1,
wherein R_1 is hydrogen.
3. A compound according to Claim 1 or
2, wherein R_2 is methyl.
4. A compound according to any one of
25 Claims 1 to 3, wherein R_3 is hydroxy or amino-carbonyl.

30

5. R,S-N-(2-Phenyl-2-hydroxyethyl)-
1-methyl-3-(4-aminocarbonylphenyl)propylamine.

6. R,S-N-(2-Phenyl-2-hydroxyethyl)-
1-methyl-3-(4-hydroxyphenyl)propylamine.

5 7. A pharmaceutical formulation comprising a compound of formula (I) as claimed in any one of claims 1 to 6, or a pharmaceutically-acceptable salt thereof, associated with a pharmaceutically-acceptable carrier therefor.

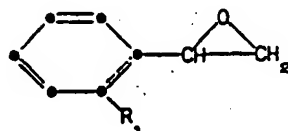
10 8. A pharmaceutical formulation as claimed in claim 7, which additionally comprises the S,S-isomer of the R,S-isomer of formula (I) as a diluent.

15 9. A compound of formula (I) as claimed in any one of claims 1 to 6 or a pharmaceutical formulation as claimed in any one of claims 7 or 8 for use in removing, or preventing the formation of, adipose tissue in mammals.

20 10. A process for preparing a compound of formula (I) as claimed in any one of claims 1 to 6, which process comprises:

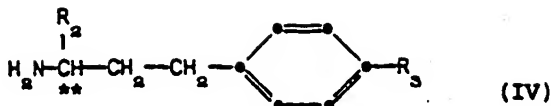
(a) reacting a styrene oxide of formula (II):

25



(II)

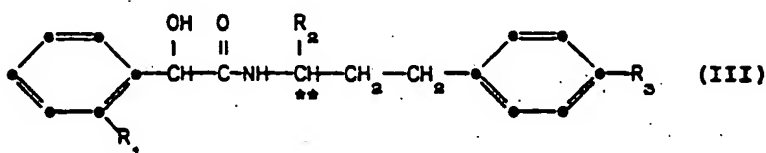
30 where R_1 is as defined in claim 1 or 2 with a propylamine derivative of formula (IV):



where R_2 and R_3 are as defined in claim 1, 3 or 4;

or

(b) reducing a compound of formula (III)



where R_1 and R_2 are as defined above and where R_3 is also as defined above or benzyl, followed in the case where R_3 is benzyl by hydrogenolysis of the benzyl group to give the compound of formula (I) where R_3 is hydroxyl; and

(c) where appropriate, resolving a product of formula (I) which is a mixture of R,S- and S,S-enantiomer.

11. A amine derivative of formula (IV) as defined in claim 10.

12. Animal feedstuff comprising a compound of formula (I) as claimed in any one of claims 1 to 6, either alone or associated with the S,S- isomer.

13. A compound of formula (I) substantially as hereinbefore described with reference to any one of the foregoing Examples.

14. A process for preparing a compound of
5 formula (I) substantially as hereinbefore described with reference to any one of the foregoing Examples.

15. A pharmaceutical formulation substantially as hereinbefore described in any one of Examples 14 to 16.

10 16. A compound of formula (I) whenever prepared by the process of claim 14.

17. A new animal feedstuff, substantially as described.

DATED THIS 3RD DAY OF JULY 1979

L. M. M. M. M.

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